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Objective Measurement of Symptoms in PD

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2.1 Advancing Parkinson's Disease: Motor and Non-Motor Fluctuations

The triad of rest tremor, slowness of movement (bradykinesia), and limb rigidity constitute the clinical hallmarks of idiopathic Parkinson's Disease (PD). However, the majority of patients will develop an increasing number of more complex symptoms over time. These symptoms include variability in the patient's mobility, so-called motor fluctuations, as well as variability in other non-motor symptoms (NMSs). Much of this variability is accounted for by a change in the patient's response to dopaminergic medication over time, such that the duration of benefit for a given dose of dopaminergic medication shortens. The following section will elaborate further on these motor and non-motor fluctuations and how they affect patients' ability to function. It is important to note, however, that not all motor fluctuations are the result of changing responses to dopaminergic medication.There is increasing recognition that several progressive motor symptoms such as postural instability and freezing of gait (FOG) are the result of non-dopaminergic dysfunction and, therefore, unlikely to respond to standard pharmacologic modifications. The clinical picture of advancing disease is further complicated by the emergence of other symptoms including cognitive dysfunction, sleep disturbances, and blood pressure instability, all of which combine to contribute to the increasing risk of falls in patients with PD. These emergent symptoms probably are a reflection of the underlying pathogenesis in PD, which is thought to involve spread of neuronal degeneration not only to dopaminergic neurons but also autonomic and cholinergic pathways. The result of advancing PD, therefore, is a tendency for patients to develop motor and non-motor fluctuations, postural

and autonomic instability, cognitive impairment, and increasing falls risk. As we shall see in the following section, the task for the clinician is to accurately document the emergence of these symptoms, so that appropriate treatment strategies may be initiated to restore patients' quality of life (QoL).

2.1.1 Motor Fluctuations

Over 70% of patients with PD will develop increasing variability in their motor response to dopaminergic treatment after 5 years [1]. These "motor fluctuations" typically appear insidiously and are often initially unnoticed by the patient. The first evidence of an emerging fluctuating medication response is the "wearing-off" phenomenon, where the patient reports slowing up or increasing stiffness as the time approaches for their next dose of medication. This commonly is apparent overnight as the patient develops difficulty turning over and getting comfortable in bed (nocturnal akinesia). Patients report that they feel the first morning dose of medication "kick in" around half an hour after taking it ("morning benefit"). Over time, patients may notice end of dose "wearing-off". This may be ultimately quite dramatic to the point where they "freeze" and become effectively immobile until such time as their next dose "kicks in". Furthermore, the time needed for the subsequent dose to start working may be strongly influenced by several factors including dietary intake of protein, which may result in a delayed time before the patient turns ON. Motor fluctuations can become so severe as to result in the ON–OFF phenomenon, where the patient may cycle rapidly between being ON (mobile) and OFF (immobile or frozen). As mentioned above, these fluctuations are the result of alterations in dopamine receptor sensitivity to exogenous dopamine. The increasingly attenuated motor response to dopaminergic medication is further complicated by an exaggerated sensitivity of the motor response, resulting in excessive involuntary movements (dyskinesia), typically during the time of peak plasma levels of dopamine. Less commonly, painful twisting (dystonic) movements occur as dopamine levels rise or fall (biphasic dyskinesia). The OFF state may be so severe in patients as to cause painful "off dystonia" or FOG. It will be apparent, therefore, that there is a wide repertoire of variability in a given patient's motor state, ranging from complete immobility to flinging choreic movements, and that these fluctuations may occur cyclically many times throughout the day. Furthermore, the occurrence of motor fluctuations is influenced by many factors, including the dose and formulation of dopaminergic drug, diet, anxiety, and use of concurrent medications. It is essential that the treating clinician documents an accurate account of these motor fluctuations, so as to guide further treatment to minimize their disruption to the patient (Table 2.1).

Table 2.1 Common motor and non-motor fluctuations in PD

Motor	Non-motor
Wearing-off	Sensory
• Morning benefit • Nocturnal akinesia • ON/OFF	• Paresthesias • Hyposmia
Freezing of gait (FOG)	Autonomic
• Start hesitation • Festination	• Sweating • Constipation • Orthostatic Hypotension
Dyskinesia	Neuropsychiatric
• Peak dose • Biphasic	• Anxiety • Depression • Psychosis
OFF dystonia	Sleep
	• Rapid eye movement (REM) sleep behavior disorder • Excess daytime sleepiness

2.1.2 Non-Motor Fluctuations

It has been increasingly recognized that while much of the day to day disability in PD relates to motor dysfunction, many patients experience a variety of NMSs, including paresthesias, fluctuating mood, and anxiety, autonomic disturbances such as constipation, postural hypotension, sleep disturbances, as well as cognitive slowing (bradyphrenia) [2, 3]. As alluded to above, many of these symptoms reflect the underlying degenerative process, which affects several neurotransmitter systems. However, it is also apparent that many of these NMSs occur as a result of dopaminergic dysregulation, and are, therefore, fluctuant in the same way as motor symptom fluctuation. NMSs typically affect one or more of four domains: neuropsychiatric, autonomic, sensory, or sleep (Table 2.1). Many NMSs are now recognized to precede the development of motor symptoms in PD, and hence, can be seen as intrinsic to the disease process. Other NMSs are likely to be due to medication effects. The importance of recognizing fluctuations in non-motor dopaminergic symptoms (such as OFF-related paresthesias or anxiety) is that their management will be entirely different to similar symptoms that may not be dopaminergic in origin. For instance, many patients will develop acute onset anxiety symptoms as the first symptom of wearing-off of their dopaminergic medication. Treatment of this symptom will involve modifications in their l-dopa intake rather than prescribing anxiolytics. It will be again apparent that it is essential for the

clinician to accurately document these symptoms so as make appropriate alterations in therapy may be made. Teasing out non-motor symptomatology can be challenging even for the experienced clinician. Adding to the complexity of this assessment is the fact that cognitive dysfunction develops in the majority of PD patients over time, so that after 15 years, 80% of patients experience significant cognitive impairment [4]. Moreover, chronic sleep disturbances due to nocturnal akinesia, rapid eye movement (REM) sleep behavior disorder and psychosis frequently result in excessive daytime somnolence. Each of these factors contributes to the difficulty that many patients have in recognizing fluctuations in MS and NMS.

2.2 Challenges in Documenting "Real-World" Fluctuating PD Symptoms

The complexity of evolving motor and non-motor fluctuations in PD poses a significant challenge to the treating clinician. It will be apparent from the previous discussion that accurate identification of true dopaminergic motor and non-motor fluctuations is paramount to the future management strategy for each patient. In the context of a busy hospital or clinic-based environment with its restrictions on the face-to-face patient time, as well as patient anxiety and fatigue, all contribute to the problem of accurate documentation of a patient's clinical status. The clinician has a number of well-worn skills at their disposal so as to become informed of how a patient is coping. The traditional history taking and detailed examination techniques provide invaluable information not only about the patient's motor function, but importantly about the patient's understanding of the different motor states. The latter is a critical aspect of the clinical encounter. Is the patient able to distinguish tremor (a manifestation of the OFF state) from dyskinesia (an ON phenomenon)? What is the patient's understanding of the terms OFF and ON? While the clinician examination will usually help in determining the patient's motor status, it is only a snapshot of a patient's daily life, and even at that, often not a particularly reliable one, as a visit to the doctor's office is not representative of a patient's daily activity, and the added burden of long travel to the clinic, a degree of patient anxiety about the encounter, as well as forgotten tablets, may all contribute to a distorted account of a patient's "real-life" clinical status.

A number of additional tools are available to help the clinician acquire the necessary data to inform therapeutic decision-making. The availability of an informed family member provides a useful narrative regarding the patient's home life, although too often the patient may live alone or a spouse

is unavailable or unable to provide helpful information. A variety of clinical rating scales and questionnaires have been developed which provide a degree of objectivity to the patient's assessment, though all have their own limitations. Although the Unified Parkinson's Disease Rating Scale (UPDRS) remains the gold standard clinical rating scale especially in a research setting, it suffers from subjectivity and variable clinician competence in using it. For many years patient diaries have provided the backbone of "real-world" interrogation of patient motor states. Diaries allow for frequent recording of a patient's motor state (OFF, ON, ON with dyskinesia; and asleep) as determined by the patient or caregiver. However, patient reported diaries are known to lack consistency and can be associated with variable adherence. In addition, patients may have physical difficulty filling in the diary due to micrographia and severe akinesia. Similarly, many patients have difficulty distinguishing tremor from dyskinesia, or may erroneously record the state they are in at the moment of documentation, rather than their predominant motor state over the preceding hour or two. What is certainly clear in relation to the accurate assessment of motor fluctuations is that the patient's motor state as determined in the clinic is rarely representative of their quotidian state; indeed, it is not uncommon for the patient to cycle from extreme akinesia to severe dyskinesias during the course of the clinic encounter. The situation regarding accurate detection of non-motor fluctuations is even more difficult, and relies mostly on obtaining a careful history from the patient and their family regarding any possible periodicity of such symptoms (Table 2.1). The NMS questionnaire [5, 6] is a 30-questions assessment tool which can be useful in highlighting symptoms not previously recognized as potentially related to PD. Such questionnaires may lack the ability to identify non-motor fluctuations as part of a medication effect and are impractical for clinical routine use.

2.3 Emerging Technologies to Monitor Symptom Fluctuations

In an attempt to improve the ability to detect and monitor the occurrence of motor fluctuations, a variety of new technologies have emerged which is beginning to transform the management of Parkinson's Disease. Two technologies have recently been combined which promise to radically change the daily management of PD: so-called "wearables" and machine-learning based techniques [7]. Suffice it to say here that these technologies can provide objective, high frequency, sensitive, and continuous data on motor and non-motor phenomena in PD [7]. In particular, the development of wearable inertial

sensors has introduced a level of objectivity in the recording of patients' motor function in daily life, so-called *free-living* monitoring [8]. The explosion of interest in the quantitative assessment and management of PD using technology-based tools has been usefully summarized in a series of reviews in the journal *Movement Disorders* [9]. Several large-scale studies on wearable technologies have reported preliminary results, along with over a dozen smaller series using a variety of machine learning algorithms for wearable sensor-based data acquisition in PD (summarized by Kubota et al. [7]). The obvious appeal of wearable technology (WT) is that it allows for community-based data acquisition over a continuous time period. In addition, the collected data is free from observer bias and the so-called attentional compensation (Hawthorne effect). The newer devices are relatively low cost with user-friendly technology. Continuous monitoring allows for the accumulation of large amounts of data, which may be analyzed at both a macro- or micro-level [10]. At a micro-level, data is available on motor state, frequency and severity of motor fluctuations, gait as well as response to medications. In the case of patients with PD, data can be acquired on the number and intensity of multiple activities, including the frequency and amplitude of movements throughout the day and night, the frequency and duration of tremor, dyskinesia, as well as impairments of gait including FOG and balance impairment [11]. There is also the possibility that detailed interrogation of data obtained at regular intervals may disclose important subclinical physiological changes that might predict a subsequent clinical change in motor state, allowing potentially for preemptive therapeutic intervention. This appears to be especially relevant in the detection of FOG [12, 13]. A big challenge, however, for any emerging sensor technology aiming to supersede existing clinical motor assessments (such as the UPDRS) is the requirement for clinimetric algorithm validation. Testing of such objective algorithms must include a test/re-test protocol to ensure reliability.

At a macro-level, general levels of activity, inactivity or sleep are available. The information obtained from WT is available both to the clinician and the patient, and importantly it allows the patient to become actively involved in their condition and learn about their level of activity as well as therapeutic efficacy. An important aspect of a WT system is that it allows remote monitoring of symptoms with its obvious potential advantage for patients and health economics (REMPARK system, presented in this book, is an example).

It should be apparent that the ability to quantify clinical phenomena using WT is not simply because "*we can*", but that the ability to reliably capture such data is a major advance on the standard qualitative clinical examination. Espay et al. [11] point out that whatever is measured must be

directed toward a therapeutic target. Despite these technological advances, however, their application in a clinical setting has been slower to evolve. As Del Din et al. [10] pointed out, there remains no gold standard against which remote monitoring WT can be compared. Moreover, simply measuring a litany of motor and non-motor phenomena should not necessarily lead to reflexly acting on such data with therapeutic intervention. What matters for one patient may cause little functional impairment for another. For instance, a common experience for the clinician is to observe a patient with severe, ballistic dyskinesias, but for whom the involuntary movements are non-disabling [14]. This dichotomy becomes even starker when one attempts to take into account various non-motor measurements (such as hyperhidrosis or anxiety), which may cause substantial disability for the patient, but remain less overt than motor recordings. A number of attempts have been made to record non-motor symptomatology using sensor technology, chiefly relating to sleep-related symptoms [15]. These sensors can provide valuable real-world insight into a variety of nocturnal sleep difficulties including RBD (REM sleep behavior disorder), nocturnal akinesia, and restless legs syndrome. Moreover, information on excessive daytime somnolence is also recordable on inertial devices. In recognition of this, several commentators have called for a "multidomain" integrated technology as the template for individualized, personalized therapeutic approach to care [11]. The REMPARK system is an attempt to provide an integrated system of personalized management of PD.

2.4 Challenges in the Use of Inertial Sensor Technology in Monitoring PD Symptoms

There exist some specific challenges in the use of technology for an objective monitoring of PD and the contribution to increase QoL of patients. A set of them are discussed below:

1. *Limitations of Motor Sensors*: Currently available commercial sensor technologies have been demonstrated to accurately measure a variety of motor symptoms in PD including tremor, bradykinesia, dyskinesia, and gait impairment [16]. However, much of the validation testing of such technology was derived from laboratory-based experimentation. Clinicians have raised a concern that this is not an accurate reflection of "real-world" situations. For example, sensor data fails to discriminate accurately whether bradykinesia is the result of fatigue, anxiety, or motor wearing-off [12]. Hence, the *context* in which sensor data is derived has a large influence on its interpretation. While the freedom to record

continuous data in an ambulatory home setting has obvious advantages over the laboratory, the trade-off is a substantial loss of experimental control over the data collection [7]. The REMPARK system and others have attempted to provide a degree of context to the sensor data by the provision of smartphone technology, which allows the patient or carer to interact with a web-based application to input subjective data, such as a non-motor questionnaire [13]. Another potential limitation of inertial sensor measurements is that their resolution may be affected by their anatomical location, and that while this may be mitigated to some extent by the application of multiple sensors, this adds to the complexity of the algorithms to interpret the data, as well as adding more complexity and discomfort for the patient [17]. Currently, most available sensors rely on single sensors applied to the most affected side in patients.

2. *NMS Monitoring*: The development of WT to monitor PD symptoms has primarily focused on motor aspects of the disease [11]. However, it has been apparent even using older established clinical scales of motor disability (UPDRS) that there is at best only a modest correlation between the degree of motor impairment and QoL. There is an emerging recognition that a substantial daily burden for patients derives from non-motor symptomatology [5], including symptoms such as anxiety, sweating, fatigue, sleep disturbances, etc. While some technologies are available to address this, such as sweat sensors, blood pressure and heart rate monitors, as well as the application of inertial sensors to monitor for sleep disturbances, clearly further refinement of this technology is needed.
3. *Clinimetrics and data validation*: There is a natural tendency to consider the development of "objective" sensor technology as ultimately replacing previously validated subjective rating scales such as the UPDRS. However, Espay et al. [11] have pointed out that the clinician integrates many sources of "data" to reach a subjective score or opinion, and that technological sensor measurements should complement clinical measures rather than act as surrogate markers.
4. *Disease Progression*: The advent of WT has opened the door to their use in clinical trials of emerging therapies as surrogate markers of efficacy. But investigators need to be cognizant that improved sensor "data" following institution of a therapy may not translate into improved QoL for patients. Moreover, use of WT longitudinally will need to take into account that PD is a progressive disease and that the parameters by which improvement must be measured will change over time. For instance, for many patients

with advanced disease, the priority of maintaining cognitive function may come at the expense of a desirable motor outcome, at which point motor sensor data becomes moot.

5. *Data Analysis*: Existing technology-based objective measures require a robust method of data analysis to ensure that the data collected is an accurate reflection of the clinical phenomena under scrutiny. The development of algorithms to appropriately interrogate the data requires close cooperation between clinicians and technical personnel. For instance, a sensor that detects "severe bradykinesia" at one measurement and "severe dyskinesia" at a second measurement within a two-minuteepoch is likely to be spurious, unless data from other sources can be factored in. In this case, the data suggesting "severe bradykinesia" is likely to be strengthened in its validity if such data is accompanied by a contemporaneous finding of "severe tremor". Development of reliable algorithms to interpret data requires input from clinicians so that appropriate weighting can be given to such data.
6. *User Engagement*: Despite enthusiasm from technologists and clinicians for the incorporation of WT into practice, current research suggests only modest patient and carer engagement [18]. Giving feedback to patients on the relevance and importance of wearing sensors seems to influence adherence.

2.5 Conclusion

There is little doubt that the rapid development of continuous WT with the ability to generate objective measurements relating to the evolving clinical state of PD patients has provided a tremendous opportunity to improve patient care, as well as learn more about the disease as it affects patients in their own environment. In the long term, these technologies will have to be sufficiently reliable and robust to allow for the remote personalized management of PD, including treatment delivery.

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